

**REMARKS**

This amendment under 37 C.F.R. § 1.111 is being submitted in response to the outstanding Official Action mailed September 4, 2002. In view of the above amendments to the Specification and Claims, the enclosed Rule 132 Declaration and the following remarks, reconsideration and allowance of this application is respectfully requested.

The specification has been amended at pages 2, 4, 7, 9 and 12 to correct obvious typographical errors. While most are self-explanatory, applicants note that at page 4, line 10, "5mm" has been changed to --5 nm--. Support for this change can be found at page 9, line 21. Likewise, at page 9, line 21 "10" microns has been changed to 100 microns. Support for this change can be found at page 4, line 10. These and the other changes to the specification do not introduce new matter.

Otherwise, claim 6 has been amended to more particularly point out and more distinctly claim the subject matter that applicants regard as the invention. In particular, claim 6 has been amended to clarify that the method mechanochemically and hydrothermally reacts the reagents simultaneously. This is disclosed in the specification at page 4, lines 12-14, which states :

The high magnesium content and high degree of magnesium substitution in the Hap lattice structure is attributable to the combined use of mechanochemical and hydrothermal process steps.

The simultaneous application of the process steps is disclosed at page 7, line 27.

Therefore, the amendment to claim 6 also does not introduce new matter. For reasons which are submitted below, the enclosed Rule 132 Declaration by one of the inventors establishes that the claims in their present form are in condition for allowance. Accordingly, reconsideration is respectfully requested.

In the Official Action, claims 6-20 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter the applicant regards as the invention. The Examiner stated, "it is not clear what limitation is intended by 'mechanochemically reacting'." This rejection is respectfully traversed for the reasons set forth hereinafter.

Applicants first note that claim 6 has not been amended in response to this indefiniteness rejection, or for any other reason related to patentability posed by the Examiner. Rather, applicants sought to better define that their inventive method relates to the simultaneous use of mechanochemical and hydrothermal processing. While this was implicit in the method as originally claimed, wherein mechanochemical processing was applied to an aqueous solution, this amendment has been made to more distinctly claim the process conditions. Clearly, it has not been made to explain the meaning of the limitation "mechanochemically reacting."

Regarding the Examiner's rejection of this term as being indefinite, applicants note that mechanochemical synthesis techniques are described in the present specification at page 3, lines 10-25. The hybrid mechanochemical-hydrothermal synthesis techniques of the present invention are described from page 3, line 17 to page 4, line 4. These techniques are also described in greater detail in the specification and demonstrated in the examples.

Entire books have been written on the subject, such as Avvakumov et al., Soft Mechanochemical Synthesis: A Basis for New Chemical Technologies (Kluwer Academic Publishers, Boston, 2001) and Gutman, Mechanochemistry of Materials (Cambridge International Publishing, Cambridge, UK, 1997). Rather than submit entire text books to the Examiner inventor, one of the inventors includes exemplary journal articles with his Rule 132

Declaration that is submitted with this amendment, as well as a copy of Chapter 4 of The Avvakumov text.<sup>1</sup>

Regardless, as explained in the enclosed Rule 132 Declaration of one of the inventors, Wojciech Suchanek, the meaning of the term “mechanochemical” is well understood and accepted by those of ordinary skill in the art as it relates to synthesis techniques. Dr. Suchanek searched “mechanochemistry” as a keyword in the Science Citation Index compiled by the Institute for Scientific Information and retrieved 1,158 scientific articles published between 1980 and October 2002 in widely accessible journals. “Mechanochemical” is clearly a term that is widely accepted by those skilled in the art.

To summarize, the meaning of the claim limitation “mechanochemically reacting” is well-understood and widely accepted by ordinarily skilled artisans. The specification, disclosure and examples provide detailed guidance regarding what a mechanochemical reaction is. One of ordinary skill in the art, having applicant’s disclosure and claims before him or her, would have a reasonable degree of certainty as to the identity of mechanochemical reaction conditions. To limit this term further would not help to define applicants’s inventive contribution and would only unnecessarily narrow the claims.

Instead, the pending claims, once read in view of the specification, fully comply with the definiteness requirements of 35 U.S.C. § 112, second paragraph with respect to the meaning of the term “mechanochemically reacting.” The meaning has been further delimited by amending the independent method claim to specify that mechanochemical and hydrothermal processes are performed simultaneously. Accordingly, reconsideration by the Examiner and withdrawal of the

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<sup>1</sup> These publications are submitted merely as evidence that the meaning of the claim limitation “mechanochemically reacting” was well-known and widely-accepted among those skilled in the art at the time the within patent application was filed. For this reason, applicants have not cited this publication in an Information Disclosure Statement, nor have the publications been listed on a Form PTO 1449 (see MPEP § 609).

rejection of claims 6-20 for the term "mechanochemically reacting" being indefinite is respectfully requested.

Turning to the prior art rejections, claims 6-8, 12-15 and 17 were rejected under 35 U.S.C. § 102(b) as being anticipated by Dolci et al., WO 00/03747. According to the Examiner, at pages 12 and 15, "Ca substituted Mg in hydroxyapatite is shown, with the instant preparation ... shown at page 21." This rejection is respectfully traversed for the reasons set forth hereinafter.

All that is disclosed at page 21 of Dolci et al. is the formation of a protective layer on apatite materials to protect them from acid attack by reacting them either in an aqueous solution containing potassium sodium tartrate and hydrous calcium acetate, or in a solution containing tartartic acid.

Page 15 of Dolci et al. discusses the replacement of some calcium ions with magnesium ions in hydroxyapatite, but not by the method that is presently claimed. What the Examiner has done here is state that the aqueous method disclosed for forming a barrier against acid attack on hydroxyapatite is also the method of the present invention when the disclosed process conditions are applied to the starting materials that are presently claimed. Granted, pages 13 and 15 disclose sources of calcium ions, phosphate ions and hydroxide ions for use in making a hydroxyapatite. But there is no disclosure regarding the addition of magnesium ions to replace calcium ions in the hydroxyapatite lattice structure.

As explained in greater detail in Dr. Suchanek's Declaration, the Dolci et al. publication neither provides any examples disclosing magnesium substitution for calcium in an apatite lattice structure at the levels produced by the process that is presently claimed, nor does it demonstrate the synthesis of magnesium-containing hydroxyapatite. On page 18, Dolci et al. states, "the nanostructured apatites according to the invention may be produced by any of the several known methods already in use for the production of noncrystalline materials." This statement is

followed by a general description of the synthesis method at pages 19-20, among which is mentioned a “mechanical attrition” method, which presumably refers to a mechanochemical method.

Dr. Suchanek points out, however, that no details are given regarding the synthesis conditions, and the method was used only to synthesize carbonated apatites, which were subsequently used in comparative tests in Examples 1 and 2. This method was not used to make magnesium containing hydroxyapatite. Furthermore, aqueous solutions are not disclosed as a reaction environment, only air, inert gas, vacuum, or liquids such as alcohols, ethers, oils and other organic molecules. Dolci et al. clearly does not disclose the hybrid mechanochemical-hydrothermal method of the present invention, and the hydroxyapatites resulting therefrom wherein magnesium is substituted for calcium in the lattice structure at the levels produced by the presently claimed process.

Dr. Suchanek further observed that on page 15, lines 12-19 DLCI et al. clearly state that in an aqueous environment, the  $Mg^{2+}$  inhibit formation of hydroxyapatite and instead promote the formation of  $\beta$ -tricalcium phosphate (TCP). With 10% of magnesium, mixtures of hydroxyapatite and TCP are formed and at 20% of magnesium only TCP is formed. This is followed by a statement that magnesium content in biological apatites is very low, about 1%.

In other words, rather than suggest the presently claimed synthesis method, Dolci et al. teaches against it, as well as the magnesium-substituted hydroxyapatite resulting therefrom. That is, as Dr. Suchanek explains, Dolci et al. suggests to those skilled in the art that high levels of magnesium incorporation into the hydroxyapatite lattice cannot be achieved from aqueous solutions.

While Dolci et al. describe a mechanochemical method to obtain carbonated hydroxyapatite, their method does not use the presently claimed aqueous solutions. Applicant's use of

aqueous solutions with at least one reagent soluble in water is what is key to the replacement of calcium ions with magnesium in the hydroxyapatite lattice structure. Until applicants discovered this critical feature it was not possible to obtain such magnesium substitution in a reproducible manner.

Because Dolci et al. does not disclose the formation of magnesium-substituted hydroxyapatite by an aqueous mechanochemical process, claims 6-8, 12-15 and 17 are not anticipated by Dolci et al. under 35 U.S.C. § 102 (b). Furthermore, because Dolci et al. contains no suggestion that aqueous mechanochemical processing would produce hydroxyapatites in which magnesium is substituted for calcium in the lattice structure, and instead teaches to the contrary that an aqueous environment's magnesium ions inhibit hydroxyapatite formation, the rejected claims are also not obvious in view of Dolci et al. under 35 U.S.C. § 103 (a). Reconsideration by the Examiner and withdrawal of this rejection is therefore respectfully requested.

Next, claims 6-20 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Jarcho in view of Ducheyne et al. Jarcho was cited as disclosing crystalline, phase-pure hydroxyapatite using diammonium phosphate as the phosphate ion source by means of a mechanochemical reaction. The Examiner acknowledges that magnesium oxide, although utilized in preparations, is not "explicitly" used to replace calcium. Ducheyne et al. was cited as disclosing a sol-gel aqueous treatment, with magnesium replacement. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art to modify the Jarcho process as shown by Ducheyne et al. "to promote Mg or other ion replacement to improve, for example, conduction property." This rejection is respectfully traversed in view of the enclosed Declaration from Dr. Suchanek for the reasons set forth hereinafter.

The Examiner considers Jarcho to disclose the mechanochemical process at column 8, lines 11-23. However, all that is disclosed at column 8 is the stirring or boiling of a hydroxyapatite suspension that was produced without the application of mechanical pressure.

As far as Ducheyne et al. is concerned, this patent is only remotely related to the preparation of hydroxyapatite. Ducheyne et al. discloses methods for increasing the biocompatibility of silica-based glass on which calcium phosphate films are formed. What Ducheyne et al. discovered was that sol-gel derived, silicon-based glass can be treated to form a calcium-phosphate surface layer without extensive degradation of the glass by immersing the glass in calcium-phosphate-containing solutions saturated in silicon. The glasses are initially prepared with biologically active molecules incorporated in the matrix. Prevention of degradation is important because degradation leads to a loss of the incorporated molecules.

The Examiner seizes upon the disclosure at column 4 around line 40 that in the calcium-phosphate-containing solutions other ions can be present, including magnesium, to conclude that this suggests the inclusion of magnesium ions in the Jarcho. However, Ducheyne et al. does not disclose the creation of hydroxyapatite layers. There is nothing to indicate what is formed on the glass surface when magnesium ions are included in the calcium-phosphate solutions.

According to Dr. Suchanek, Jarcho has nothing to do with the mechanochemical synthesis of hydroxyapatite. Dr. Suchanek notes that the disclosure at column 8 relied upon the Examiner describes a process in which a calcium-phosphate precipitate is only being stirred at room temperature for 24 hours. Dr. Suchanek states that the use of high-energy equipment (described in the present specification) is necessary to accomplish the hybrid mechanochemical-hydrothermal synthesis of the present invention.

Dr. Suchanek further elaborates that the room temperature process described by Jarcho is widely used in the world and documented in the scientific literature as a process known to produce either amorphous calcium phosphate or hydroxyapatite with a very low crystallinity that is often strongly non-stoichiometric. Because mechanochemical hydrothermal techniques are not used, the Jarcho method fails to produce the fairly crystalline and highly stoichiometric hydroxyapatite that is obtained by the presently claimed method.

Addressing Ducheyne et al., Dr. Suchanek notes that the presence of magnesium ions in solution during precipitation of calcium-phosphate phases on the glass surface. He notes, however, that Ducheyne et al. do not specify which calcium-phosphate is formed, and states that this is understandable for those skilled in the art, because the films are difficult to characterize and various calcium-phosphate phases could form.

According to Dr. Suchanek, Ducheyne et al.'s conclusion in Example 4 that carbonate-hydroxyapatite is inferred from FTIR observations based upon P-O vibrations located at 560 and 604  $\text{cm}^{-1}$  and a C-O band at 870, and is an overstatement. Dr. Suchanek states that hydroxyapatite is just one of the possible phases that exhibits such FTIR vibrations, citing page 33 of LeGeros, Calcium Phosphates in Oral Biology and Medicine (Karger AG, Basel, Switzerland, 1991). He states that octacalcium phosphate has P-O vibrations in the same positions, and there is also  $\text{HPO}_4^{2-}$  derived band overlapping with C-O around 870  $\text{cm}^{-1}$ . He concludes that, to those skilled in the art, there is no evidence of hydroxyapatite phase formation disclosed by Ducheyne et al.

Dr. Suchanek further states that Ducheyne et al. do not show any evidence of magnesium substitution for calcium in the lattice of the calcium-phosphate layers. According to Dr. Suchanek, to those having ordinary skill in the art it is obvious from the widely accepted knowledge of magnesium effects on the precipitation of various calcium-phosphates from aqueous solutions, as reviewed by the above-cited LeGeros at pages 79-80 and 97-99 and by Elliot, Structure and Chemistry of the Appetites and Other and Calcium Orthophosphate (Elsevier) at pages 44-45 and 53- 54, that, under the condition described by Ducheyne et al., the presence of magnesium ions in the solution stabilizes either the amorphous calcium-phosphate phase or the whitlockite phase. Dr. Suchanek states that even if hydroxyapatite did form, for which he noted there was no clear evidence, the level of magnesium substitution, is extremely small, about 0.4% weight percent. From all of this Dr. Suchanek concludes that there is no disclosure in Ducheyne et al. that would suggest to one of ordinary skill in the art how to achieve



magnesium substitution for calcium in a hydroxyapatite lattice at the levels obtained by the presently claimed method.

Because Jarcho does not disclose the mechanochemical processing of calcium-phosphate to form hydroxy appetite, let alone a hybrid mechanochemical-hydrothermal process, and Ducheyne et al. discloses at best the use of low levels of magnesium ion in a process that is not mechanochemical, claims 6-20 therefore parentally distinguish over this cited combination of prior art under 35 U.S.C. § 103 (a). Reconsideration by the Examiner and withdrawal of this rejection is therefore respectfully requested.

Applicants note that the Office Action Summary states that claims 6-20 and 29 are pending in the application and subject to the species election that was made, but only states that claims 6-20 are rejected. This is consistent with pages 2-4 of the Official Action, in which none of the rejections are applied to claim 29. However, there is no further mention of claim 29, either as being allowed, even though claim 29 is an independent claim. Clarification by the Examiner regarding the status of claim 29 is respectfully requested.

Finally, the Examiner states "the journal article was not present; please provide." Presumably this refers to the Bigi et al. journal article listed on the Form PTO-1449 submitted with the March 5, 2001 Information Disclosure Statement that was filed. A replacement copy of that article is enclosed with this amendment.

Otherwise, in view of the above amendments to the specification and claims, the enclosed Rule 132 Declaration, and the foregoing remarks this application is now in condition for allowance. Reconsideration is respectfully requested. Attached hereto is a marked-up version of the changes made to the specification and claim 6 by the current amendment. The attached paper is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Applicant(s): Riman et al.  
Application No. 09/800,127  
Page 15

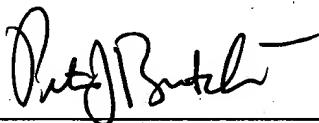
Docket No. P24,186 USA

The Examiner is requested to telephone the undersigned if it is believed that there are any remaining issues in this application to be resolved. Finally, if there are any additional charges in connection with this response, the Examiner is authorized to charge applicants' Deposit Account No. 19-5425 therefor.

Respectfully submitted,

Dated

February 3, 2003



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the Specification**

The paragraph at page 2, lines 12-19 has been amended as follows:

Increasing concentration of ~~Mg~~ Mg in HAp has the following effects on its properties: (a) gradual decrease in crystallinity, (b) increase HPO<sub>4</sub> incorporation, and (c) increase in extent of dissolution. Magnesium is closely associated with mineralization of calcified tissues, and indirectly influences mineral metabolism. It has been suggested that magnesium directly stimulates osteoblast proliferation with an effect comparable to that of insulin (a known growth factor for osteoblast). Thus, it becomes possible to tailor the physicochemical properties of HAp, as well as its biocompatibility and bioactivity, by controlling the Mg substitution of the HAp lattice structure.

The paragraph at page 4, lines 5-11 has been amended as follows:

Therefore, according to one aspect of the present invention, a stable, phase-pure magnesium-substituted crystalline hydroxyapatite is provided containing from about 2.0 to about 29 wt% magnesium, wherein at least 75 wt% of the magnesium content is substituted for calcium ions in the hydroxyapatite lattice structure. The Mg-HAp of the present invention forms as crystal agglomerates. The present invention therefore also includes particles of the Mg-HAp of the present invention having a particle size between about ~~5mm~~ 5 nm and about 100 microns.

The two paragraphs extending from page 7, line 19 to page 8, line 5 have been amended as follows:

With stirring of the aqueous slurry/solution, the ion sources are mechanochemically reacted, typically by the application of physical force to the water-insoluble ion sources or

insoluble apatite precursors that are suspended as a slurry in the aqueous reaction medium containing the water-soluble ion sources. Preferred mechanochemical reaction processes comminute the ion source slurry particles, preferably by milling or grinding the water insoluble ion source particles with heating of the aqueous reaction medium into which the water-soluble ion source has been dissolved. Preferred methods at the same time frictionally heat the aqueous reaction medium/slurry while the slurry particles are being milled or ground, so that the mechanochemical and hydrothermal ~~process step~~ processes are performed simultaneously.

Multi-ring media mills are preferred. ~~The grinding mechanism consists~~ which consist of a central rotating stainless steel shaft, which drives a plurality of stainless steel sub-shafts (sleeve-lined with zirconia-toughened alumina) that are connected symmetrically to the central shaft. Each sub-shaft contains a plurality of stacked zirconia rings, which rotate eccentrically around each sub-shaft. When the central shaft is rotating, the zirconia rings on the sub-shafts are moved by the centrifugal force radially outwards, applying force on the inner wall of the milling vessel, which is ceramic lined. Solid slurry particles located between the rotating rings and the liner wall are consequently comminuted.

At page 9, please replace the two paragraphs at lines 17-29 with the following two paragraphs:

The crystalline Mg-HAp will have a magnesium content between about 2.0 and about 29 wt%, with levels between about 3.5 and about 28.4 wt% being preferred. Levels between about 5 and about 25 wt% are even more preferred, with a level of at least 10 wt% being most preferred. The crystalline Mg-HAp of the present invention forms crystals agglomerates having ~~an~~ approximate particles ranging in approximate size between about 5 nm and about ~~10~~ 100 microns.

The crystalline Mg-HAp of the present invention is useful in the preparation of compounds for use as granular fill for direct incorporation into the hard tissues of humans or other animals, and as bone implantable materials. The present invention thus includes granular fill compounds, bone implant materials, tooth filling compounds, bone cements and dentifrices containing the Mg-HAp of the present invention. The products are formulated and prepared by substituting the Mg-HAp of the present invention for HAp in conventional HAp-based products. The compounds may be prepared from in the form of metallic and polymeric Mg-HAp composites.

At page 12, please replace the paragraph at line 2-11 with the following paragraph:

**Example 2 - Mechanochemical-hydrothermal synthesis of  $\text{Ca}_7\text{Mg}_3(\text{PO}_4)_6(\text{OH})_2$**

$\text{Ca}(\text{OH})_2$ , ~~Mg~~  $\text{Mg}(\text{OH})_2$  and solid  $(\text{NH}_4)_2\text{HPO}_4$  (analytical grade, Alfa Aesar, Ward Hill, MA) were used as reactants for the synthesis of Mg-HAp. First, a suspension containing a powdered mixture of 19.150 g  $\text{Ca}(\text{OH})_2$  and 6.717 g  $\text{Mg}(\text{OH})_2$  in 350 mL of deionized water was prepared inside a 500 mL glass beaker. Subsequently, 29.028 g of  $(\text{NH}_4)_2\text{HPO}_4$  powder was slowly added to the same beaker at constant vigorous stirring using a magnetic stirrer for about 10 min. The (Ca+Mg)/P molar ratio in the starting slurry was 1.67. The presence of water adsorbed on all reactants was measured by thermogravimetry to maintain the targeted stoichiometries. The pH of the slurry was about 10.2, measured using a glass electrode connected to a pH-meter (Accumet Model 805 MP, Fisher Scientific, Pittsburgh, PA) and calibrated with respect to a buffer solution (pH=10.00, Fisher Scientific).

The paragraph extending from page 12, line 22 to page 13, line 2 has been amended as follows:

The washed solid phase was dried in an oven at 70°C for 24 h (Isotemp oven, model 230G, Fisher Scientific) and ground into powder. The synthesized ~~Mg~~ Mg-HAp powder